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Preliminary findings of the clinical utility of an fMRI approach to visuospatial memory lateralization in paediatric and adult patients with epilepsy

A. Marsh[1,2,3], O. Keating[2,3], E. Brooks[2,3], & I. Wright[1,2,3]

1. Department of Neuropsychology, North Bristol NHS Trust. 2. School of Experimental Psychology, University of Bristol.[3.] Department of Paediatric Neuropsychology, University Hospitals Bristol NHS FT.

Introduction

fMRI methods are increasingly used in the pre-surgical study of focal epilepsy patients. Data obtained regarding the lateralisation of memory and the assessment of the functional integrity of brain structures is important for predicting cognitive outcome following surgical resection of epileptogenic tissue. Current paradigms for assessing **memory lateralisation have largely focussed on verbal memory,** which reliably recruit left hemisphere structures. The development of **visuospatial paradigms has proved more challenging** with left hemisphere processing biases and verbalisation strategies preventing development of a right hemisphere task. The current task aimed to determine the merit of a **newly-designed visuospatial paradigm** in maximising BOLD asymmetry to the right by **placing a preferential load on spatial memory.**

Methods

Both healthy controls (*n* = 20, age *M* = 24.7 years, range = 18-40) and 10 patients *(see below Table 1) with **temporal lobe epilepsy** underwent a **forced-choice visuospatial recognition** task that **tested memory for orientation of a novel stimulus**, whilst undergoing **fMRI**. The experiment involved an **encoding** (WATCH) phase, a **retrieval** (CHOOSE) phase and a **rest** phase (see example images on the right). During encoding trials, participants had to attend to novel visual stimuli and were asked to pay particular attention to the spatial layout. Stimuli were presented in blocks of 20 consecutive images. Subsequent recognition blocks were presented comprising 8 images from the immediately preceding block and images from earlier blocks. **Behavioural data was recorded** through the presentation software (Neurobehavioural Systems) and test **performance scores were explored** for both healthy controls and patient samples. **fMRI data was obtained** using a 3T Siemens Skyra MRI Scanner with standard 20 channel head and neck coil. The functional scans consisted of 250 volumes collected using gradient-echo echo-planar imaging (EPI) with a TR=2800 ms, TE=30ms and 90 degree flip angle. 40 contiguous axial slices were collected, with 3mm thickness, 192 mm field of view and a voxel size of 3x3x3mm. T1 structural scans were also obtained (192 volumes) with a 256 x 256 matrix, voxel size 1x1x1 mm.

**Only 6 patients scans were able to be analysed due to scan acquisition difficulties, such as too much movement artefact.*

Table 1. Patient Demographics

Pt	Age & Gender	Onset	Duration	Handedness	Pathology Features	Left Activation *M* (*SD*)	Right Activation *M* (*SD*)	Left vs Right Significance	Laterality Index (LI)	Lateralisation
P1G	51.4 M	5.4	46	R	Left hemispheric temporal abnormalities on MR and sharp wave spikes on right EEG	EN = .09 (.09) RE = .19(..15)	EN = .66 (.10)) RE = -.14 (.27)	EN *p*=.0001** RE *p*=.0001**	EN = -0.76 RE = +0.13	EN = R RE = BI
P2E	12.9 M	2.5	10.3	L	Left temporal lesion	EN = -.11 (.89) RE = -.31 (.70)	EN = -.08 (.64) RE = .05 (.57)	EN *p*=.0001** RE *p*= .0001**	EN = +0.16 RE = +1.42	EN = NA RE = L
P3F	12.2 F	8.4	3.8	L	Left anteromesial temporal lobe resection	EN = -.35 (.12) RE = -.09(.67)	EN = -.30 (.17) RE = .19 (.72)	EN *p*= .2538 RE *p*= .0001**	EN = +0.07 RE = -2.83	EN = NA RE = R
P4J	22.1 M	U/K	U/K	R	Resection of left tentorium meningioma	EN = -.18 (.41) RE = -.34 (.57)	EN = -.21 (.48) RE = -.18 (.47)	EN *p*= .0172* RE *p*= .0001**	EN = -0.09 RE = +0.29	EN = NA RE = NA
P5C	31.1 M	21	10.1	R	Shrunken left hippocampus	EN = -.00 (.36) RE = .08 (.31)	EN = .09 (.59) RE = .29 (.57)	EN *p*= .0001** RE *p*= .0001**	EN = -1.02 RE = -0.56	EN = R RE = R
P6H	56.2 F	9	47.2	R	Sharp wave spikes within right on EEG	EN = .07 (.43) RE = -.01 (.84)	EN = -.13 (.49) RE = .22 (.76)	EN *p*= .2662 RE *p*= .0001**	EN = -3.38 RE = -1.08	EN = R RE = R

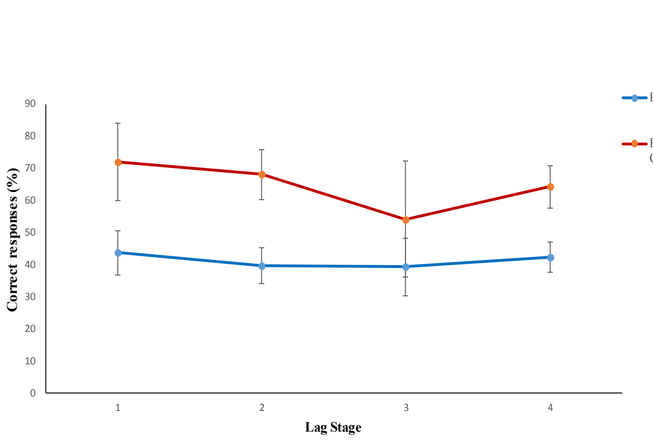

Figure 3. Performance of participants y lag stage on MMT

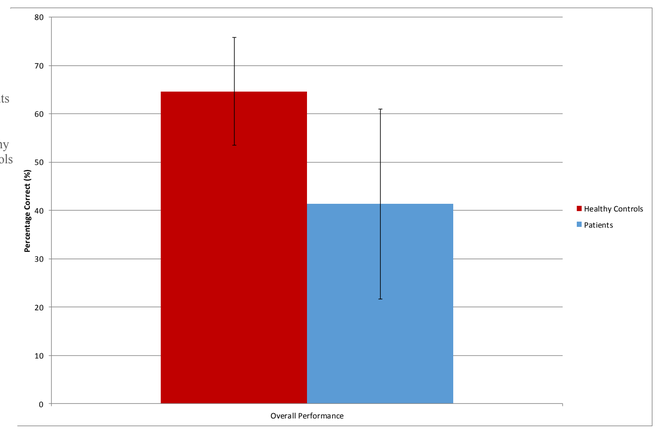

Figure 3. Average performance of controls versus patients on MMT

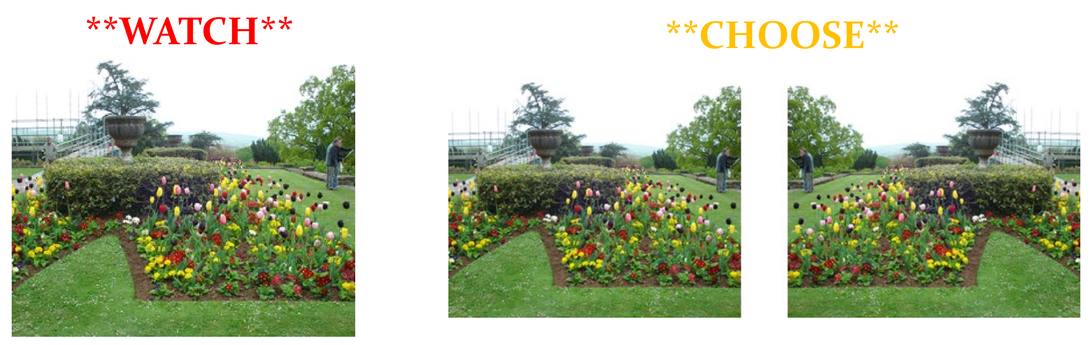

Figure 1. Example of Mirror Memory Task

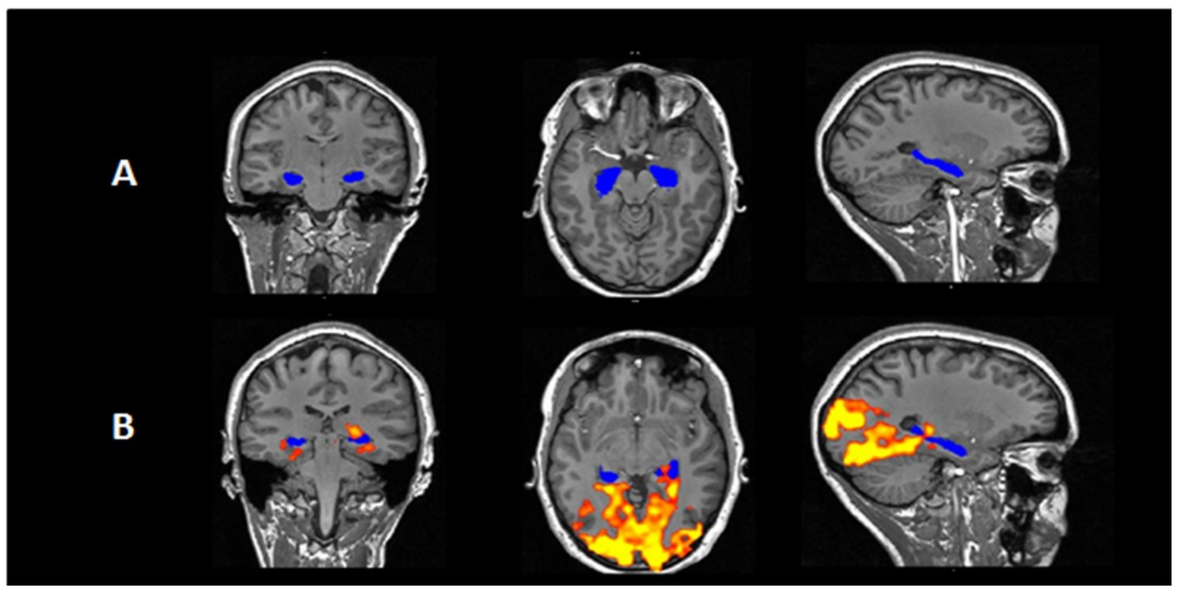

Figure 2. Single participant's activation maps for scene encoding (24, -18, -27). (A) Anatomical segmentation of the hippocampi in blue, (B) activation map for the main effect of scene encoding in red-yellow

Analysis

fMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool), part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). **Registration to high resolution structural** and/or standard space images was carried out using FLIRT (Jenkinson, 2001; 2002). **Time-series statistical analyses** were carried out using defined **models examining encoding/retrieval versus rest**, with local autocorrelation correction (Woolrich, 2001). Participant specific T1 was **co-referenced with a MNI152 T1 2mm brain**, which was used to co-register the BOLD signal. Standard motion parameters were applied and MCLFIRT **motion correction** was used with spatial smoothing set at 5mm. Z (Gaussianised T/F) statistic **images were thresholded using clusters (*z* = 2.3)** and a (corrected) cluster significance threshold of *p* = 0.05 (Worsley, 2001). **ROI analysis was conducted** using FSL Expert Analysis Tool v6.00 - FEAT Query with the aid of The Harvard-Oxford Cortical Atlas to define ROIs (right/left hippocampus). **T-tests** were used to examine **differences between the right and left ROIs**.

Total percentage correct for **behavioural data** were calculated and **t-tests** were used to **examine differences in performance between healthy controls and patient samples**.

Results

- **Behavioural analysis** (see *Figure 3)* demonstrated **healthy controls** (*M*=64.6 *SD*=11.1), **performed significantly better** (*p<.05)* on the mirror memory task **than the patient sample** (*M*=41.3, *SD*=19.7), with no individuals in either group hitting near ceiling (100% correct) or floor (0% correct) for performance.

- In **healthy controls**, **successful recruitment of right hippocampus** was demonstrated **during spatial encoding** of visual scenes (see *Figure 2.*), with the right hippocampus being activated significantly more than the left ($p<0.001$) and region of interest analysis demonstrating right-sided dominance (LI = -9.11). However, there were no differences between left and right hippocampal activation on retrieval ($p>0.05$).

- Preliminary findings for patient data are presented in Table 1. Global deactivation of hippocampal regions were seen in some patients, therefore lateralisation could not be determined. For all remaining patients with **s left temporal pathology, the MMT encoding phase demonstrated right hippocampal dominance for visuospatial memory**, as would be predicted. The results were more inconsistent for the retrieval phase, similar to that for controls.

Conclusions and Future Directions

- This paradigm stimulated significant activation of the right versus left hippocampus, demonstrating right-temporal dominance for encoding of visuospatial information in healthy controls
- 7 of the 12 controls demonstrated deactivation of their hippocampal regions during retrieval phase. This is likely a consequence of poor signal to noise ratio and poor model fit. This may be accounted for by failed encoding, and thus retrieval, of tested stimuli that therefore would not have recruited hippocampal regions. Future research might focus on using behavioural data to generate a more specific event related design that examines only retrieval phases that were first successfully encoded.
- Further future directions would include:
  - Improving sample sizes of both clinical cases and healthy controls
  - Recruiting patients with clear right sided-pathology
  - Further definition of clinical groups into early and late onset of seizure, within the left and right groups to better predict likelihood of neuroplasticity.
  - Exploring predictive validity of LI results using pre and post-operative visuospatial memory performance data following right/left temporal resection
  - Interrogating verbal memory areas and then using these to define parameters to better control for verbalisation strategies